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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,863	06/27/2003	Ryoichi Hashida	3462.1003-000	8202
21005	7590	05/13/2005	EXAMINER	
HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			HOWARD, ZACHARY C	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 05/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/608,863	<b>Applicant(s)</b> HASHIDA ET AL.	
	<b>Examiner</b> Zachary C. Howard	<b>Art Unit</b> 1646	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 February 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-53 is/are pending in the application.
- 4a) Of the above claim(s) 4-30 and 32-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>6/7/04; 11/22/04</u> . | 6) <input type="checkbox"/> Other: _____  |

*pd*

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election of Group I, claims 1-3 and 31, in the reply filed on 2/14/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4-30 and 32-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3 and 31 are under consideration.

### ***Specification***

The portion of the current title that reads "...and therapeutic agents for treating same" is not descriptive because it describes a non-elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "Method of testing for atopic dermatitis by measuring expression of the NOR-1 gene."

### ***Information Disclosure Statement***

The information disclosure statement filed 6/7/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.

Specifically, there is no copy of references AM (cited as EP 1287019, 11/22/2001); AO (cited as EP 1265628, 9/27/01); or AQ (cited as EP 1185647, 12/21/2000). Therefore, these citations on the IDS of 6/7/2004 have been crossed out and Applicant is requested to submit these references with a new Information

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Disclosure Statement. The examiner notes that copies of all of the other references cited on the IDS of 6/7/2004 and the IDS of 11/22/2004 are present and have been considered.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claim 1 is such that the claimed method encompasses testing for any allergic disease by measuring the expression level of the NOR-1 protein or gene in eosinophils of a test subject. Claim 2 limits the process of measuring to cDNA PCR and claims 3 and 4 limit the allergic disease to atopic dermatitis.

Applicants teach the gene expression level (copy/ng RNA) of the NOR-1 gene in the eosinophil cells of seven patients in the exacerbation and remission stages of atopic dermatitis. Individual values are reported and range from 53-3745 copy/ng RNA in the exacerbation stage, and 167-5298 copy/ng RNA in the remission stage. Averages are

not provided, but are easily calculated: 934 for the exacerbation stage, and 2342 for the remission stage. As these results indicate, there is significant variation between the individual scores and the average. Applicants further teach that the average level of gene expression level of the NOR-1 gene in the eosinophils of five healthy patients is 960 copy/ng RNA. Applicants do not provide individual scores for the healthy individuals, or present the range of the healthy scores. Furthermore, while Applicants have provided a statistical analysis of the results with exacerbation and remissions stage subjects, Applicants do not provide any statistical analysis of the results for any of the subjects with atopic dermatitis and the healthy subject. Based on the results, Applicants assert that a test for atopic dermatitis can be performed by the measuring level of expression of the NOR-1 gene and comparing this result with the level in a healthy subject. However, a skilled artisan would not be able to use this method without further experimentation because Applicants do not teach what level of NOR-1 gene expression indicates that atopic dermatitis is present. The method requires measurement of NOR-1 gene expression in a test subject to determine if the subject has atopic dermatitis or is healthy. The specification appears to teach that, if NOR-1 gene expression was measured and showed significant variation from the healthy average of 960, one would conclude that an individual had atopic dermatitis. However, the amount of variation of NOR-1 gene expression in the healthy subjects is not provided. Based on the amount of variation seem in the atopic dermatitis patients, a skilled artisan would conclude that the results with healthy subjects would also variation. Therefore, a measurement that varied from 960 would misdiagnose a healthy individual as having atopic dermatitis. In order to use the method, a skilled artisan would first need to engage in undue experimentation to determine the range of values for healthy individuals and determine if this is significantly different than individuals with atopic dermatitis.

Even if the claims were enabled for a method of testing for the remission stage of atopic dermatitis, they would not provide enablement for testing for the exacerbation stage of atopic dermatitis, or for any other allergic disease. The results provided by Applicants' results show that average level of NOR-1 gene expression in individuals in

the exacerbation stage of atopic dermatitis is identical to that of healthy individuals. Therefore, it is not possible to use the method to distinguish between subjects in the exacerbation stage of atopic dermatitis from healthy subject. Furthermore, Applicants have not shown the level of NOR-1 gene expression in any other allergic disease. As stated above, Applicants have not enabled a method to distinguish subjects with either the exacerbation or remission stage from healthy individuals. Applicants' own results with the exacerbation stage of atopic dermatitis show that there are allergic disease conditions that cannot be tested for with this method. Therefore is it not predictable whether or not this method could be used to distinguish between subjects with any other allergic disease and healthy individuals.

Furthermore, the claims 1 and 3 encompass diagnosis by measuring the level of NOR-1 protein. Even if the invention were enabled for a diagnostic method by measuring NOR-1 gene expression it would not be enabled for a diagnostic method directed to measuring specific protein levels. The diagnostic method disclosed in the specification showed results relating to gene expression, not protein expression. It is well known in the art that gene expression is not an accurate predictor of protein expression (see page 1863, section 2.1 of Haynes et al, 1998, Electrophoresis. 19(11): 1862-1871). Protein expression does not always reflect the expression level of the gene encoding the protein. Regulation of the rate translation initiation could produce a different level of protein synthesis; furthermore, the rate of protein degradation could be different. Therefore, the method disclosed is not enabled for a diagnostic method using protein expression.

For the reasons set forth, without further guidance a person of ordinary skill in the art would not be able to make and/or use the invention as claimed without undue experimentation. Due to the large quantity of experimentation necessary to determine if the method could be used to diagnostically, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided

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is a mere wish or plan and an invitation to experiment to determine whether the method could be used to test for atopic dermatitis or other allergic diseases.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear how comparing the responses leads to the identification required by the preamble. Clarity could be added to the claim by adding at the end a phrase such as, "wherein \_\_\_\_\_ (e.g. atopic dermatitis) is indicated by an increase in the level of \_\_\_\_\_ (e.g. NOR-1 gene expression) in the eosinophil cells of a test subject as compared with a healthy subject. Note that there must be basis in the specification for the type of response and the suggestions made by the examiner do not necessarily have basis but are intended to present the general idea of concepts that may be suitable.

Claims 2, 3, and 31 are indefinite because they depend from rejected claim 1 and do not add clarity to the method.

***Note***

It is noted that the prior art does not disclose a sequence that is 100% identical to the NOR-1 polynucleotide of SEQ ID NO: 1.

U.S. Patent No. 6812339 discloses a polynucleotide sequence (SEQ ID NO: 3789) that is 99.6% identical to instant SEQ ID NO: 1 and encodes a protein that is 100% identical to instant SEQ ID NO: 2 (which is the NOR-1 polypeptide encoded by SEQ ID NO: 1).

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The prior art does not teach expression of a NOR-1 gene or protein in eosinophil cells in healthy subjects or subjects with an allergic disease, or a method of testing for atopic dermatitis by comparing the level of expression of a test subject with the expression level of a healthy subject.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER